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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/762,568	07/30/2001	Atsushi Katsumata	HIKARI.001APC	5060

20995 7590 08/19/2004

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EXAMINER

SULLIVAN, DANIEL M

ART UNIT PAPER NUMBER

1636

DATE MAILED: 08/19/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

## Office Action Summary

**Application No.**

09/762,568

**Applicant(s)**

KATSUMANTA ET AL.

**Examiner**

Daniel M Sullivan

**Art Unit**

1636

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --  
**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

### Status

- 1) ☒ Responsive to communication(s) filed on 03 August 2004.  
2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.  
3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

### Disposition of Claims

- 4) ☒ Claim(s) 1,2,4-8 and 15-18 is/are pending in the application.  
4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.  
5) ☒ Claim(s) 1,2 and 4-7 is/are allowed.  
6) ☒ Claim(s) 8 and 15-18 is/are rejected.  
7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.  
8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

### Application Papers

- 9) ☐ The specification is objected to by the Examiner.  
10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).  
11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

### Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).  
a) ☐ All b) ☐ Some \* c) ☐ None of:  
1. ☐ Certified copies of the priority documents have been received.  
2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.  
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

### Attachment(s)

- 1) ☐ Notice of References Cited (PTO-892)  
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)  
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)  
Paper No(s)/Mail Date \_\_\_\_\_.  
4) ☐ Interview Summary (PTO-413)  
Paper No(s)/Mail Date. \_\_\_\_\_.  
5) ☐ Notice of Informal Patent Application (PTO-152)  
6) ☐ Other: \_\_\_\_\_.

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### **DETAILED ACTION**

This Non-Final Office Action is a reply to the Paper filed 3 August 2004 in response to the Final Office Action mailed 1 June 2004. The 3 August Paper has been entered and **finality of the previous Office Action is hereby withdrawn**. Claims 16-18 had been previously withdrawn from consideration and claims 1, 2, 4-8 and 15 were considered in the 1 June Office Action. Claims 2, 4, 8 and 15 were amended in the 3 August Paper.

### ***Response to Amendment***

#### Allowable Subject Matter

Claims 1, 2 and 4-7 are allowed.

#### Election/Restrictions

Claim 2 is directed to an allowable product. Pursuant to the procedures set forth in the Official Gazette notice dated March 26, 1996 (1184 O.G. 86), claims 16-18, directed to the process of making or using the patentable product, previously withdrawn from consideration as a result of a restriction requirement, are now subject to being rejoined. Claims 16-18 hereby rejoined and fully examined for patentability under 37 CFR 1.104.

Since all pending claims previously withdrawn from consideration under 37 CFR 1.142 have been rejoined, the restriction requirement among Groups I, III and IV made in the Office action mailed on 16 July 2003 is hereby withdrawn.

Claims 1, 2, 4-8 and 15-18 are presently under consideration.

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Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 8 and 15 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an isolated host cell having introduced therein the plasmid vector according to claim 2 and a method for producing a useful substance in an isolated host cell, does not reasonably provide enablement for a transgenic chicken cell. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Although it was previously indicated that the claims were enabled for a transgenic chicken expressing a GFP transgene, and a method for expressing GFP in a transgenic chicken, upon further consideration, it is clear that the disclosure does not adequately enable making a transgenic animal such that it can be used as contemplated in the specification. With regard to using a transgenic chicken, the only utility contemplated in the specification is the production of a useful substance, which is particularly described as production in eggs (see especially the discussion beginning in the paragraph bridging pages 44-45 and continued through the second full paragraph on page 49). Although the disclosure teaches how to make a transgenic chicken having measurable GFP expression in lymphocytes, the specification does not teach a real-world use for the chicken reduced to practice. No evidence is provided that the transgene is expressed in the eggs of the chicken in any useful quantity and for reasons of record and herein below, one of ordinary skill in the art would not expect to be able to produce useful quantities of transgene

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in the chicken without additional manipulations requiring undue experimentation. Furthermore, the specification does not provide a real-world use for the transgenic chicken or the lymphocytes expressing GFP obtained therefrom which are actually reduced to practice. Therefore, the transgenic chicken cell of the claims is not enabled over any scope.

Claims 16-18 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include, but are not limited to: (a) the nature of the invention; (b) the breadth of the claims; (c) the state of the prior art; (d) the amount of direction provided by the inventor; (e) the existence of working examples; (f) the relative skill of those in the art; (g) whether the quantity of experimentation needed to make or use the invention based on the content of the disclosure is "undue"; and (h) the level of predictability in the art (MPEP 2164.01 (a)).

*Nature of the invention and Breadth of the claims:* The claims are directed to a method for producing a useful substance in an egg of a transgenic bird comprising providing the plasmid vector of claim 2. As the claim generally encompasses the production of any protein in an egg laid by a bird, the specification must teach the skilled artisan how to practice the invention such that it can be used as contemplated in the specification without undue experimentation.

*Amount of direction provided by the inventor and existence of working examples:* The instant disclosure describes a plasmid vector comprising both an integrase gene operably linked to a promoter and an integrase recognition region, which facilitates integration of the plasmid vector into the genome of a host cell (see throughout). In the examples, Applicant demonstrates: a method of integrating a vector into the genome of a cell line transfected with the vector (Example 2); a method of integrating a vector into the genome of somatic and germline cells of chickens by injecting the vector into embryos (Example 3), and germline transmission of the vector (Example 6); a method of expressing a feline G-CSF protein in a cultured cell line by the method of introducing a vector comprising a nucleic acid encoding G-CSF (Example 4); and a method of expressing a marker gene (i.e., GFP) in transgenic chickens comprising injecting a vector comprising GFP into embryos.

The specification provides a discussion directed to heterologous expression of proteins in the eggs of transgenic chickens (see especially the discussion beginning on page 45 and continued through page 49). However, using the full scope of the claimed methods requires that the skilled artisan is able to obtain expression of a useful substance regardless of the substance produced. Thus, in order to use the full scope of the claimed method, the skilled artisan must extend the teachings of the specification—which are limited to general statements that the claimed transformants can be used to produce useful substances, an example of a cell line expressing G-CSF, and an example of a transgenic chicken expressing GFP in lymphocytes—to obtain expression of any useful substance from the egg of a transgenic bird.

*State of the prior art and level of predictability in the art:* With regard to the production of useful substances in transgenic animals, at the time of the effective filing date of the instant

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application (*i.e.*, 27 April 2000) the useful production of recombinant proteins in any animal was in an early stage of development. In reviewing the relevant literature, Houdebine (2000) *Transgen. Res.* 9:305-320 describes a myriad of obstacles that have been encountered by artisans seeking to express recombinant proteins in mammals, a relatively well developed system, at pharmaceutically relevant levels. In the abstract, Houdebine identifies three major sources of unpredictability in the art. First is the unpredictability of transgene expression; second is the unpredictability of proper posttranslational modification; and third is the unpredictable effects of high-level recombinant expression on the host mammal. Significantly, in an article published at the time the instant application was filed, Houdebine teaches, “the mammary gland is presently the only really available animal bioreactor” (page 315, column 1, paragraph 7). Thus, at the time of filing, methods for useful production of recombinant proteins were limited mammary gland.

Houdebine points out that experiments carried out *in vitro* using cultured cells are poor predictors of expression *in vivo*. In the third paragraph in the first column on page 314, Houdebine states, “[cultured mammary] cells can at best predict the intrinsic potency of a construct for transcription but not the level of expression in transgenic animals. The cell lines are not expected to be able to reflect all the events, which mature the proteins post-transcriptionally.” Houdebine further teaches that proper posttranslational processing of proteins expressed at levels that would be considered useful is often unpredictable because the mechanisms are dependent on cellular enzymes that are present at variable concentrations in different cell types (paragraph bridging columns 1 and 2 on page 313). Importantly, because proper glycosylation is vital for pharmacological activity of many proteins, Houdebine teaches that mammary cells do not always glycosylate recombinant proteins in an appropriate manner even when the protein is naturally

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secreted in milk in a glycosylated form (see the example of bile salt-stimulated lipase presented in the second full paragraph in the right column on page 313). Houdebine teaches that the reasons why some proteins are not correctly glycosylated are particularly complex and might be related to the superphysiological production of the recombinant protein.

When viewed as a whole, the teachings of Houdebine, which are based on a review of the art at the time instant application was filed, clearly show that obtaining useful expression of a protein in a transgenic bioreactor was only enabled for a limited set of proteins in mammary tissues, and production of pharmaceutically useful amounts of any given protein even in mammary tissue was unpredictable.

With regard to production of a useful substance in hen eggs, it is reasonable to expect that the sources of unpredictability encountered in more established transgenic bioreactor systems (i.e., unpredictability of transgene expression, unpredictability of proper posttranslational modification and unpredictable effects of high-level recombinant expression on the host animal; *Id.*) would also be encountered in birds. Furthermore, in an article published recently, Ivarie (2003) *Trends Biotechnol.* 21:14-19, teaches that expressing an protein at a useful level in eggs is particularly difficult because “[a] highly expressed oviduct promoter has not been developed” (page 16, second full paragraph in the left column). Further, Ivarie teaches “[t]he retroviral methods, although useful in proof-of-principle experiments, might not be able to deliver large enough constructs for high level, tissue-specific expression of pharmaceuticals in oviduct cells” (second full paragraph in the right column on page 17). Thus, Ivarie clearly teaches that production of useful substances in hen eggs, regardless of the vector used, was far from routine at the time the instant application was filed.

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*Relative skill of those in the art and quantity of experimentation needed to make or use the invention:* Although the relative level of skill in the art is high, one of ordinary skill in the art would not be able to practice the claimed methods of producing a useful substance without having to engage in undue experimentation. With regard to the transformant, the disclosure provides a vector that can be used to transform cells and make transgenic animals, and describes a transgenic chicken expressing a GFP reporter gene in lymphocytes. However, the art establishes that producing any substance in a transgenic chicken such that it is useful as contemplated in the specification is highly unpredictable. As the teachings of the instant specification do nothing to address the sources of unpredictability in methods encompassing transgenic bioreactors (i.e., unpredictability of transgene expression, unpredictability of proper posttranslational modification and unpredictable effects of high-level recombinant expression on the host animal), practicing the full scope of the claimed method requires that the skilled artisan engage in empirical experimentation to provide the additional method steps required to obtain useful expression of each unique substance. Again, the level of experimentation required would be well beyond what is routine in the art.

For these reasons, the claims fail to meet the enablement requirement of 35 U.S.C. §112, first paragraph.

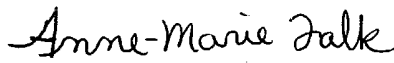
### ***Conclusion***

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Daniel M Sullivan whose telephone number is 571-272-0779. The examiner can normally be reached on Monday through Thursday 6:30-5:00.

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If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel, Ph.D. can be reached on 571-272-0781. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

  
ANNE-MARIE FALK, PH.D.  
PRIMARY EXAMINER

Daniel M Sullivan, Ph.D.  
Examiner  
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